Citation:

Mason JB, Dickstein A, Jacques PF, Haggarty P, Selhub J, Dallal G, Rosenberg IH. A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: A hypothesis. *Cancer Epidemiol Biomarkers Prev*. 2007 Jul; 16 (7): 1,325-1,329.

Worksheet created prior to Spring 2004 using earlier ADA research analysis template.

PubMed ID: 17626997

Study Design:

Trend study

Class:

D - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

This research hypothesis highlights a temporal association between folic acid fortification of enriched cereal grains in the United States and Canada and an increase in the incidence of colorectal cancer (CRC) in these two countries. This paper presents a hypothetical foundation on which further research will be required to determine whether causality exists.

Inclusion Criteria:

- Any individual included in either of the following:
  - In the United States, the nationwide Surveillance, Epidemiology and End Result registry (which collects cancer incidence and survival data from population-based cancer registries covering ~26% of the US population
  - In Canada, the Canadian Cancer Statistics, 2006, which is published annually by the Canadian Cancer Society and the National registry of cancer incidence and mortality maintained by the Health Statistics Division at Statistics Canada.
- In the United States, individuals participate in the National Behavioral Risk Factor Surveillance System (conducted by the CDC).

Exclusion Criteria:

Any individual who is not included in the databases mentioned in Inclusion Criteria.

Description of Study Protocol:

Recruitment

Nationally representative data were collected from:

- United States: The nationwide Surveillance, Epidemiology and End Result registry, which collects cancer incidence and survival data from population-based cancer registries covering ~26% of the US population
- Canada: the Canadian Cancer Statistics, 2006, which is published annually by the Canadian Cancer Society and the National registry of cancer incidence and mortality maintained by the Health Statistics Division at Statistics Canada.

Design

Trend Study (hypothesis).

Dietary Intake/Dietary Assessment Methodology

Not applicable.

Intervention

Folic acid fortification.

Statistical Analysis

- Excess CRC incidence rates in US and Canada calculated as deviations from linear regressions based on the years preceding the institution of voluntary fortification (1986-1995 trend in US and 1986-1996 trend in Canada). A non-parametric loess smoother was fitted to the data and 95% CI bands were drawn by using PROC LOESS of SAS for Windows, version 9.1.2, with its default settings
- Endoscopy rates (for US only based on the CDC Prevention Behavior Risk Factor Surveillance System surveys) reported as percentage of respondents (no N given)
- Parametric and non-parametric curve fitting procedures were done but neither could adequately capture the apparent sharp bends in the data associated with the implementation of folic acid fortification.

Data Collection Summary:

- *Timing of measurements:* One-time data collaction (using population-based registries)
- *Dependent variables***:** Colorectal Cancer (CRC)
- *Independent variables:* Folic acid fortification of enriched cereal grains
- *Control variables:* Controlled for the rate of colorectal endoscopic procedures.

Description of Actual Data Sample:

- *Initial N:* Unclear—only incidence rates given (no actual numbers)
- *Attrition (final N):* Unknown
- *Age:* Not reported
- *Ethnicity:* Not described
- *Other relevant demographics:* None
- *Anthropometrics:* Unknown
- *Location:* United States and Canada.

Summary of Results:

- The United States and Canada experienced abrupt reversals of the downward trend of colorectal cancer (CRC) incidence that the two countries had enjoyed in the decade preceding mandatory fortification of enriched cereal grains with folic acid
- In the US the absolute rates of CRC began to increase in 1996 and peaked in 1998
- In Canada the absolute rates of CRC began to increase in 1998 and peaked in 2000
- Both countries have continued to exceed the pre-1996-1997 trends by four to six additional cases per 100,000 individuals
- In each country the increase in CRC incidence from the prefortification trend falls significantly outside of the downward linear fit based on non-parametric 95% CI
- Increase in rates remain statistically significant when data from each country were analyzed separately for men and women
- Changes in colorectal endoscopic procedures do not seem to account for this increase in CRC incidence.

Author Conclusion:

This communication is a hypothesis highlighting the need for further research to determine whether folic acid fortification was responsible for the increase in CRC rates in the US and Canada. The authors stress the need for better monitoring and further research in this field.

Reviewer Comments:

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes

4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	N/A
2.3.	Were health, demographics, and other characteristics of subjects described?	No
2.4.	Were the subjects/patients a representative sample of the relevant population?	???
3.	**Were study groups comparable?**	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	???

4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	???
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	No
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A

7.	**Were outcomes clearly defined and the measurements valid and reliable?**		Yes
	7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
	7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A
	7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
	7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
	7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
	7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
	7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**		Yes
	8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
	8.2.	Were correct statistical tests used and assumptions of test not violated?	???
	8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes